1409768

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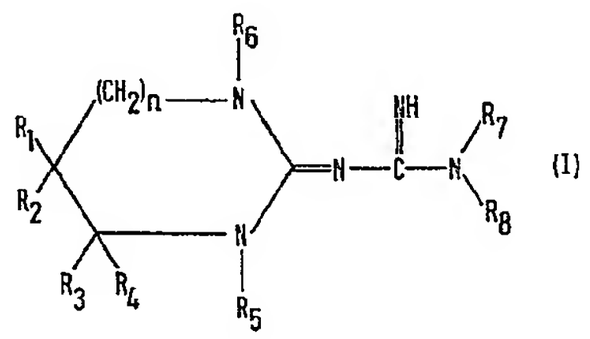
(19) 

(54) HETEROCYCLIC DERIVATIVES OF GUANIDINE

(71) We, DR. KARL THOMAE G.M.B.H., a German Body Corporate, of Biberach an der Riss, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to performed, to be particularly described in and by the following statement:—

This invention relates to new heterocyclic derivatives of guanidine having interesting pharmacological properties and to a process for the preparation thereof.

According to one feature of the present invention there are provided compounds of the general formula



(I)

[wherein R_1 and R_2 which may be the same or different, represent hydrogen atoms or straight chain or branched chain alkyl groups containing from 1 to 4 carbon atoms, or one of the groups R_1 and R_2 represents a hydroxyl group and the other of the groups R_1 and R_2 is as hereinbefore defined; R_3 and R_4, which may be the same or different, represent hydrogen atoms or straight chain or branched chain alkyl groups containing from 1 to 4 carbon atoms;

R_5 represents a hydrogen atom, a straight chain or branched chain alkyl group containing from 1 to 6 carbon atoms, a hydroxyalkyl group containing 2 or 3 carbon atoms, a phenyl group optionally mono- or di-substituted by alkyl or alkoxy groups containing 1 or 2 carbon atoms, by fluorine, chlorine or bromine atoms or by nitrile groups, a benzyl or phenylethyl group optionally mono- or di-substituted by halogen atoms, or an adamantyl group;

R_6 represents a hydrogen atom or a straight chain or branched chain alkyl group containing from 1 to 4 carbon atoms;

R_7 represents a hydrogen atom, a straight chain or branched chain alkyl group containing from 1 to 6 carbon atoms, a hydroxyalkyl group containing 2 or 3 carbon atoms, a benzyl or phenylethyl group optionally substituted by halogen atoms or by alkyl or alkoxy groups containing 1 or 2 carbon atoms, a phenyl group optionally substituted by chlorine atoms or by carboxyl or aminosulphonyl groups, or an adamantyl group; and

R_8 represents a hydrogen atom or a straight chain or branched chain alkyl group containing from 1 to 4 carbon atoms; or

R_7 together with R_8 and the nitrogen atom to which they are attached represent a 5-, 6- or 7-membered saturated heterocyclic ring, which may, if desired, be interrupted by an oxygen or sulphur atom or by another nitrogen atom, optionally substituted by an alkyl group containing from 1 to 3 carbon atoms or by a phenyl group; and

n=0 or 1] and acid addition salts thereof.

The new compounds of the present invention are therefore derivatives of imidazolidine and of hexahydropyrimidine. Suitable saturated heterocyclic rings which may be formed by the groups R_7 and R_8 together with the nitrogen atom to which they are attached are, for example pyrrolidine, piperidine, morpholine, thiomorpholine, piperazine and hexamethyleneimine rings.

The new compounds according to the invention exhibit interesting pharmacological properties. In general they have an antimicrobial action, especially when applied locally, and a virucidal action. In addition they

will usually induce a lowering of the blood sugar level.

Preferred compounds according to the present invention, by virtue of their especially favourable pharmacological properties include:—

2 - [3 - (β - phenylethyl) - guanidinylidene] - imidazolidine and physiologically acceptable acid addition salts thereof,

1 - methyl - 2 - [3 - (β - phenylethyl) - guanidinylidene] - imidazolidine and physiologically acceptable acid addition salts thereof,

2 - (3 - butyl - guanidinylidene) - imidazolidine and physiologically acceptable acid addition salts thereof,

1 - (β - phenylethyl) - 2 - guanidinylidene - imidazolidine and physiologically acceptable acid addition salts thereof,

1 - methyl - 2 - guanidinylidene - imidazolidine and physiologically acceptable acid addition salts thereof,

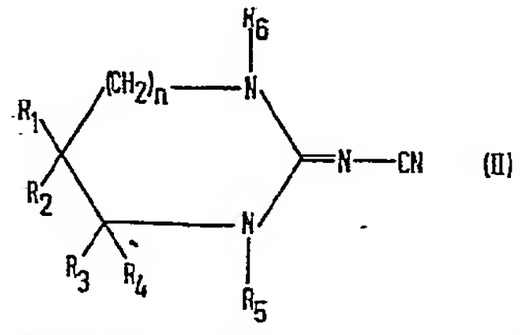
1 - ethyl - 2 - (3 - butyl - guanidinylidene) - imidazolidine and physiologically acceptable acid addition salts thereof,

1 - butyl - 2 - (3 - butyl - guanidinylidene) - imidazolidine and physiologically acceptable acid addition salts thereof,

1 - (3,4 - dichlorobenzyl) - 2 - (3 - guanidinylidene) - imidazolidine and physiologically acceptable acid addition salts thereof, and

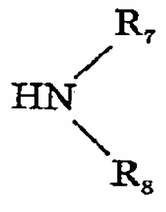
1 - butyl - 2 - (3 - butyl - guanidinylidene) - hexahydropyrimidine and physiologically acceptable acid addition salts thereof.

According to a further feature of the present invention there is provided a process for the preparation of compounds of the present invention which comprises reacting a cyanimino compound of formula



(II)

[wherein R_1 to R_6 and n are as hereinbefore defined] with an amine of formula

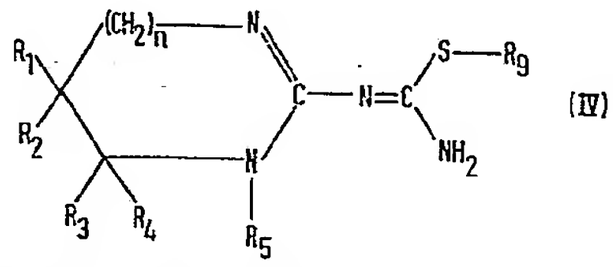


III

[wherein R_7 and R_8 are as hereinbefore defined] or preferably with an acid addition salt of the said amine, in particular a hydrochloride.

The reaction is preferably carried out at temperatures of from 80°C to 220°C in a solvent-free melt or in the presence of a solvent, for example in water, methyl pyrrolidone, dimethylformamide, quinoline or butanol. The reaction generally results in the direct precipitation of the acid addition salt of a compound of formula I (as hereinbefore defined). This salt may be purified by the usual methods and if desired may subsequently be converted into the free base. A particularly efficient method of purifying the imidazolidine derivatives of formula I comprises converting them into their sparingly soluble crystallisable copper complexes which are then dissolved in a dilute mineral acid, and the copper present in the solutions is removed by precipitation with hydrogen sulphide.

According to a still further feature of the present invention there is provided a process for the preparation of compounds of general formula I (wherein R_1 to R_5, R_7 and R_8 are as hereinbefore defined and R_6 represents a hydrogen atom) which comprises reacting an S-alkylthiourea of the general formula IV



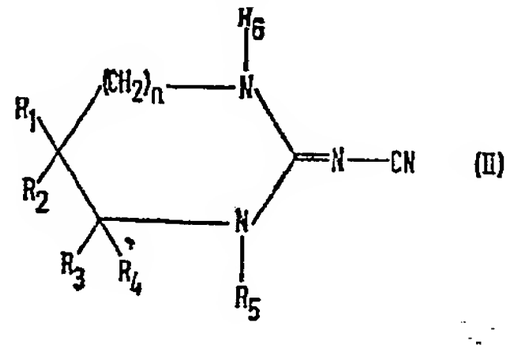
(IV)

(wherein R_1 to R_5 and n are as hereinbefore defined and R_9 represents an alkyl group) or an acid addition salt thereof, advantageously the hydrohalic acid addition salt with an amine of general formula III.

The reaction is conveniently carried out in the presence of an anhydrous solvent, preferably in the presence of an alcohol such as methanol, ethanol or propanol, at temperatures of from 40°C to 150°C, preferably at temperatures of from 50°C to 100°C. If desired, the reaction may be effected in the presence of an excess of the amine of general formula III, which excess acts as solvent.

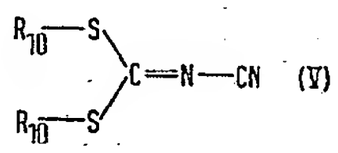
The free bases of general formula I may, if desired, be converted into their physiologically acceptable acid addition salts with inorganic or organic acids by the usual methods.

The compounds of general formula



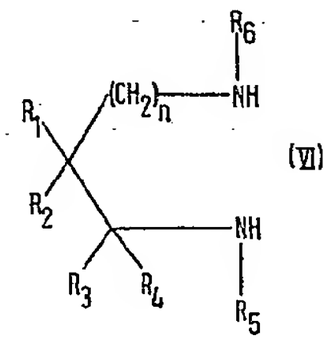
(II)

(wherein R_1 to R_6 and n are as hereinbefore defined) may be obtained by reacting an N-cyanimino-dithiocarbonic acid ester of general formula



(V)

wherein the R_{10} groups, which may be the same or different, represent alkyl groups or together represent an ethylene group) with a compound of general formula



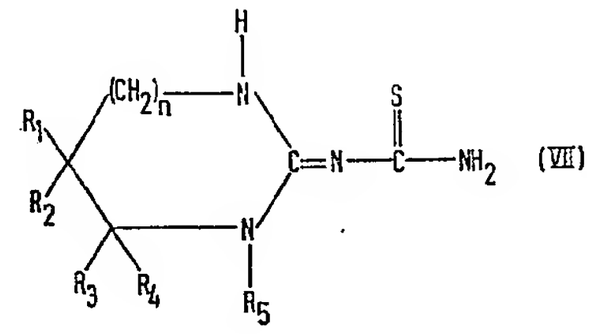
(VI)

(wherein R_1 to R_6 and n are as hereinbefore defined).

The reaction may be carried out in a solvent-free melt or in the presence of a solvent. Suitable solvents are, for example, diethyl ether, alcohols containing from 1 to 3 carbon atoms and dimethylformamide. The reaction in the melt is usually carried out at temperatures of from 150°C to 200°C. It may suitably be carried out in the presence of inorganic or tertiary organic bases, for example, alkali metal amides, alkali metal hydrides, calcium oxide, trialkylamines or pyridine, but is preferably carried out in the presence of a heavy metal oxide such as lead (II) oxide or mercury (II) oxide.

The compounds represented by formulae V and VI are known and may be obtained by methods known from the literature. N - Cyaniminodithiocarbonic acid esters of the formula V, for example, may be prepared by the method according to Hantzsch, (Annalen *331* [1904], 282—288), while the amines of formula VI may be prepared by the method of Frost, (J. Org. Chem. *24*, [1959], 1581—1582).

The S - alkyl - 1 - imidazolinyl - thioureas and S - alkyl - 1 - hexahydropyrinidyl - thioureas of general formula IV used as starting materials may be obtained, for example, by reacting known 2 - cyanimino - imidazolidines and hexahydropyrimidines with hydrogen sulphide under pressure to produce 2 - thiocarbamoylimino - imidazolidines and hexahydropyrimidines of general formula



(VII)

(wherein R_1 to R_5 are as hereinbefore defined) which are then converted into the compounds of general formula IV, for example, by means of alkyl iodides.

As previously stated, the compounds of formula I according to the present invention usually induce a lowering of the blood sugar level. Compounds which have been tested have thus been found to inhibit the reabsorption of glucose, lower the rate of gluconeogenesis and have a potentiating action on insulin in the utilisation of glucose by muscular tissue. The tested compounds have proved particularly effective in animals suffering from obesity (KK-mouse).

The blood sugar lowering activity of the new compounds of formula I was tested by the following methods:

a) Measurement of the reduction in blood sugar level in fasting guinea-pigs after administration of relatively small doses and removal of blood samples by cardiac puncture.

b) Measurement of the lowering of blood sugar level in fasting rats after administration of relatively high doses and removal of blood samples by ocular puncture or puncture of the tail.

c) Measurement of the drop in blood sugar level after the rise following a glucose test carried out on fasting rats after three days administration of medium concentrations of the compounds. The blood sugar concentration was measured 15, 30 and 60 minutes after intraperitoneal administration of glucose. In this test, a rapid return of the blood sugar concentration to a low level compared with the time taken in control animals indicates a positive effect.

Methods a) and b) are standard methods; measurements in these tests were taken over an observation time of up to 5 hours after application. Method c) was described by W. Losert and coworkers in a lecture given to the 5th Congress of the German Diabetic Association, Bonn, 1970.

In some of the tests mentioned above, the new compounds were found to be significantly superior to phenylethyl - biguanide which is known in the literature.

The new compounds of formula I were tested for their antimicrobial action by the agar diffusion test and the serial dilution test based on the method described by P. Klein

in "Bakteriologische Grundlagen der Chemotherapeutischen Laboratoriumspraxis", Springer Verlag 1957, pages 53—76 and 87—109.

According to a still further feature of the present invention there are provided pharmaceutical compositions comprising as active ingredient at least one compound of formula I as hereinbefore defined or a physiologically acceptable acid addition salt thereof in association with a pharmaceutical carrier or excipient.

Compositions according to the invention for antimicrobial use are usually administered topically and are conveniently presented in the form of ointments, tinctures, creams and lotions. Antidiabetically-active compositions according to the invention are conveniently administered orally and are generally presented in the form of tablets and coated dragées.

Advantageously the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. For oral administration each dosage unit preferably contains from 20 to 100 mg of active ingredient. The total daily dose is preferably 60 to 200 mg.

For topical application the concentration of active ingredient is preferably from 0.5 to 5% by weight of the pharmaceutical composition.

The following Examples 1 to 104 serve to illustrate the preparation of compounds of general formula I according to the present invention.

Examples of the preparation of the starting compounds:

Example A

2-Cyanimino-imidazolidine

200 ml of ethylenediamine and 150 ml of chloroform were mixed in a 3-necked flask and a solution of 50 g (0.34 mol) of N - cyanimino - dithiocarbonic acid dimethyl ester was added with stirring and at such a rate that the temperature remained at about 40—45°C.

After addition of all the N - cyanimino - dithiocarbonic acid dimethyl ester, stirring was continued for another half hour and the solvent and excess ethylenediamine were then distilled off *in vacuo*. The residue was recrystallised from ethanol.

Yield: 75% of theory; m.p. 210°C.

Analysis:

Calculated:	C 43.63	H 5.49	N 50.89
Found:	43.75	5.42	51.20

The following compounds may be prepared in analogous manner:

Example B

1 - Methyl - 2 - cyanimino - imidazolidine
Melting point: 138°C.

Example C

1 - Phenylethylamino - 2 - cyanimino - imidazolidine
Melting point: 123°C.

Example D

1 - Ethyl - 2 - cyanimino - imidazolidine
Melting point: 108°C.

Example E

1 - Butyl - 2 - cyanimino - imidazolidine
Melting point: 63°C.

Examples of preparation of compounds of formula I and acid addition salts thereof according to the present invention:

Example 1

2 - [3 - (β - Phenylethyl) - guanidinylidene] - imidazolidine

5.5 g (0.05 mol) of 2 - cyanimino - imidazolidine were vigorously mixed with 7.85 g (0.05 mol) of β - phenylethylamine hydrochloride and the mixture was heated for 20 minutes on an oil bath preheated to 150°C. The resulting melt was cooled, dissolved in water and poured into excess ammoniacal copper sulphate solution. The crystalline copper complex which precipitated was filtered off at the pump and washed several times with water. It was then dissolved in 2N hydrochloric acid, filtered to remove any undissolved particles and treated with hydrogen sulphide. The copper sulphide which formed was filtered off and the solvent was removed from the filtrate on a rotary evaporator. The residue was recrystallised from ethanol.

Yield: 33% of theory; melting point 208°C (dihydrochloride).

Analysis:

Calculated:	C 47.40	H 6.26	N 23.02
Found:	47.50	6.34	23.12

Example 2

2 - [3 - (3,4 - Dichlorobenzyl) - guanidinylidene] - imidazolidine

Prepared from 2 - cyanimino - imidazolidine and 3,4 - dihclorobenzylamine hydrochloride analogously to Example 1.

Oil bath temperature: 170°C.

Yield: 22% of theory; melting point 223°C (dihydrochloride).

Analysis:

Calculated:	C 36.80	H 4.20	Cl 39.50
Found:	36.85	4.18	39.40

Example 3

1 - Methyl - 2 - [3 - (β - phenylethyl) - guanidinylidene] - imidazolidine

Prepared from 1 - methyl - 2 - cyanimino - imidazolidine and β - phenylethylamine hydrochloride analogously to Example 1.

Oil bath temperature: 140°C; time: 2 hours.

Yield: 41% of theory; melting point: 160°C (dihydrochloride).

Analysis:

Calculated:	C 49.10	H 6.64	N 22.00
Found:	48.90	6.77	22.35

Example 4

1 - Methyl - 2 - [3 - (3,4 - dichlorobenzyl) - guanidinylidene] - imidazolidine

Prepared from 1 - methyl - 2 - cyanimino - imidazolidine and 3,4 - dichlorobenzylamine hydrochloride according to Example 1.

Yield: 26% of theory; melting point: 189—191°C (dihydrochloride).

Analysis:

Calculated:	C 38.65	H 4.60	N 18.77
Found:	38.90	4.70	18.70

Example 5

2 - (3 - Butyl - guanidinylidene) - imidazolidine

Prepared from 2 - cyanimino - imidazolidine and butylamine hydrochloride according to Example 1.

Oil bath temperature: 150°C; time: 15 minutes,

Yield: 23% of theory; melting point: 177—178°C (dihydrochloride).

Analysis:

Calculated:	C 37.52	H 7.48	N 27.33
Found:	37.70	7.58	27.30

Example 6

1 - Methyl - 2 - [3 - (4 - chlorophenyl) - guanidinylidene] - imidazolidine

1.70 g (10.36 mmol) of *p* - chlorophenylamine hydrochloride, 1.24 g (10.0 mmol) of 1 - methyl - 2 - cyanimino - imidazolidine and 5 ml of water were refluxed for 1 hour. The mixture was cooled and a crystalline paste precipitated out. This paste was filtered at the pump, washed several times with water and recrystallised from water.

Yield: 17% of theory; melting point: 225—226°C (hydrochloride).

Analysis:

Calculated:	C 45.80	H 5.25	N 24.30
Found:	45.90	5.25	24.40

Example 7

1,3 - Dimethyl - 2 - [3 - (3,4 - dichlorobenzyl) - guanidinylidene] - imidazolidine

Prepared from 1,3 - dimethyl - 2 - cyanimino - imidazolidine and 3,4 - dichlorobenzylamine hydrochloride.

Oil bath temperature: 140°C; time: 80 minutes.

Isolation: The melt was recrystallised directly from isopropanol.

Yield: 48% of theory; melting point: 211—212°C (hydrochloride).

Analysis:
Calculated:
C 44.50 H 5.17 Cl 30.36 N 19.97
Found:
C 44.40 H 5.24 Cl 30.70 N 19.55

Example 8

1 - Methyl - 2 - (3 - butyl - guanidinylidene) - imidazolidine

Prepared from 1 - methyl - 2 - cyanimino - imidazolidine and butylamine hydrochloride according to Example 1.

Oil bath temperature: 145°C; time: 2 hours.

Yield: 38% of theory; melting point: 175—179°C (dihydrochloride).

Analysis:

Calculated:	C 40.04	H 7.82	N 25.91
Found:	40.10	7.86	26.20

Example 9

2 - [3 - (4 - Chlorophenyl) - guanidinylidene] - imidazolidine

Prepared from 2 - cyanimino - imidazolidine and *p* - chloroaniline hydrochloride according to Example 6.

Yield: 63% of theory; melting point 217—218°C (hydrochloride).

Analysis:

Calculated:	C 43.75	H 4.77	N 25.54
Found:	43.70	4.92	25.20

Example 10

1 - [β - Phenyl - ethyl] - 2 - [3 - (4 - chlorophenyl) - guanidinylidene] - imidazolidine

Prepared from 1 - (β - phenyl - ethyl) - 2 - cyaniminoimidazolidine and *p* - chloroaniline hydrochloride according to Example 6.

Yield: 74% of theory; melting point: 221—222°C (hydrochloride).

Analysis:

Calculated:	C 57.20	H 5.59	N 18.50
Found:	57.50	5.48	18.80

Example 11

1 - [β - Phenyl - ethyl] - 2 - (3 - β - phenyl-ethyl - guanidinylidene) - imidazolidine

Prepared from 1 - (β - phenyl - ethyl) - 2 - cyanimino - imidazolidine and β - phenyl - ethylamine hydrochloride according to Example 1.

Yield: 40% of theory; melting point: 132°C (after recrystallization from methyl ethyl ketone) (hydrochloride).

Analysis:

Calculated:	C 64.60	H 7.05	N 18.82
Found:	64.80	6.96	18.90

Example 12

1 - [β - Phenyl - ethyl] - 2 - [3 - (3,4 - dichlorobenzyl) - guanidinylidene] - imidazolidine

Prepared from 1 - (β - phenyl - ethyl) - 2 - cyanimino - imidazolidine and 3,4 - dichlorobenzylamine hydrochloride.

Oil bath temperature: 150°C; time: 15 minutes.

Isolation: The melt was extracted with chloroform and 2N hydrochloric acid and the layers were separated. The chloroform was distilled off and the residue was recrystallised from methyl ethyl ketone.

Yield: 43% of theory; melting point; 180°C (hydrochloride).

Analysis:

Calculated:	C 53.47	H 5.20	N 16.41
Found:	53.60	5.30	16.60

Example 13

1 - [β - Phenyl - ethyl] - 2 - (3 - butyl - guanidinylidene) - imidazolidine

Prepared from 1 - (β - phenyl - ethyl) - 2 - cyanimino - imidazolidine and butylamine hydrochloride according to Example 12.

Yield: 22% of theory; melting point; 155°C (hydrochloride).

Analysis:

Calculated:	C 59.33	H 8.09	N 21.62
Found:	59.60	7.76	21.75

Example 14

5 - Hydroxy - 2 - [3 - (4 - chlorophenyl) - guanidinylidene] - hexahydropyrimidine

Prepared from 5 - hydroxy - 2 - cyanimino - hexahydropyrimidine and *p* - chloroaniline hydrochloride according to Example 6.

Yield: 44.5% of theory; melting point: 195—197°C (hydrochloride).

Analysis:

Calculated:	C 43.43	H 4.97	N 23.02
Found:	43.60	4.89	22.85

Example 15

5 - Hydroxy - 2 - (3 - methyl - guanidinylidene) - hexahydropyrimidine

Prepared from 5 - hydroxy - 2 - cyanimino - hexahydropyrimidine and methylamine hydrochloride.

Oil bath temperature: 170—180°C; time: 20 minutes.

Isolation: The melt was triturated with isopropanol and the precipitate obtained was filtered off under suction and recrystallised from ethanol.

Yield: 15% of theory; melting point: 197—199°C (hydrochloride).

Analysis:

Calculated:	C 34.69	H 6.79	N 33.72
Found:	34.90	6.81	33.50

Example 16

5 - Hydroxy - 2 - (3,3 - dimethyl - guanidinylidene) - hexahydropyridine

Prepared from 5 - hydroxy - 2 - cyanimino - hexahydropyridine and dimethylamine hydrochloride according to Example 15.

Oil bath temperature: 170—180°C; time: 20 minutes.

Yield: 18% of theory; melting point: 212—214°C (hydrochloride).

Analysis:

Calculated:	C 37.92	H 7.27	N 31.59
Found:	38.15	7.37	31.50

Example 17

1 - (2 - Hydroxyethyl) - 2 - [3 - (β - phenyl - ethyl) - guanidinylidene] - imidazolidine

Prepared from 1 - (2 - hydroxyethyl) - 2 - cyanimino - imidazolidine and β - phenyl - ethylamine hydrochloride according to Example 1.

The dihydrochloride was obtained as an oil.

Analysis:

Calculated:	C 48.29	H 6.65	N 20.12
Found:	47.50	6.60	19.57

Example 18

2 - (3,3 - Dimethyl - guanidinylidene) - imidazolidine

Prepared from 2 - cyanimino - imidazolidine and dimethylamine hydrochloride according to Example 7.

Oil bath temperature: 150°C; time: 15 minutes.

Yield: 50% of theory; melting point: 255°C (hydrochloride).

Analysis:

Calculated:	C 37.59	H 7.36	N 36.54
Found:	37.80	7.47	36.25

Example 19

2 - (3 - Methyl - guanidinylidene) - imidazolidine

Prepared from 2 - cyanimino - imidazolidine and methylamine hydrochloride according to Example 1.

Oil bath temperature: 180°C; time: 20 minutes.

Yield: 26% of theory; melting point: 218°C (dihydrochloride).

Analysis:

Calculated:	C 28.00	H 6.07	N 32.77
Found:	28.15	6.11	33.12

Example 20

1,3 - Dimethyl - 2 - [3 - (4 - chlorophenyl) - guanidinylidene] - imidazolidine

Prepared from 1,3 - dimethyl - 2 - cyan-

imino - imidazolidine and *p* - chloroaniline hydrochloride according to Example 6.

Yield: 66% of theory; melting point: 216—217°C (after recrystallization from isopropanol) (hydrochloride).

Analysis:

Calculated:	C 47.70	H 5.67	N 23.18
Found:	48.00	5.66	22.60

Example 21

1 - Butyl - 2 - [3 - (4 - chlorophenyl) - guanidinylidene] - imidazolidine

Prepared from 1 - butyl - 2 - cyanimino - imidazolidine and *p* - chloroaniline hydrochloride according to Example 6.

Yield: 79% of theory; melting point: 198.5—200°C (hydrochloride).

Analysis:

Calculated:	C 50.85	H 6.40	N 21.20
Found:	50.60	6.31	21.11

Example 22

1 - [β - Phenyl - ethyl] - 2 - guanidinylidene - imidazolidine

Prepared from 1 - (β - phenyl - ethyl) - 2 - cyanimino - imidazolidine and ammonium chloride according to Example 1.

Oil bath temperature: 200°C; time: 20 minutes.

Yield: 9% of theory; melting point: 184—186°C (dihydrochloride).

Analysis:

Calculated:	C 47.35	H 6.29	N 23.00
Found:	47.30	6.26	22.85

Example 23

1 - Butyl - 2 - [3 - (β - phenyl - ethyl) - guanidinylidene] - imidazolidine

Prepared from 1 - butyl - 2 - cyanimino - imidazolidine and β - phenyl - ethylamine hydrochloride according to Example 1.

Oil bath temperature: 150°C; time: 2 hours.

Yield: 54% of theory; melting point: 114—115°C (dichloride).

Analysis:

Calculated:	C 53.30	H 7.55	N 19.44
Found:	53.50	7.65	19.67

Example 24

1 - Ethyl - 2 - [3 - (4 - chlorophenyl) - guanidinylidene] - imidazolidine

Prepared from 1 - ethyl - 2 - cyanimino - imidazolidine and *p* - chloroaniline hydrochloride according to Example 6.

Yield: 48% of theory; melting point: 207—208°C (hydrochloride).

Analysis:

Calculated:	C 47.70	H 5.67	N 23.15
Found:	47.50	5.47	23.40

Example 25

1 - Methyl - 2 - guanidinylidene - imidazolidine

Prepared from 1 - methyl - 2 - cyanimino - imidazolidine and ammonium chloride according to Example 1. The dihydrochloride was obtained as a vitreous mass.

Oil bath temperature: 150°C; time: 2 hours.

Yield: 7.2% of theory.

Analysis:

Calculated:	C 28.03	H 6.12	N 32.70
Found:	28.50	6.26	32.05

Example 26

1 - Ethyl - 2 - guanidinylidene - imidazolidine

Prepared from 1 - ethyl - 2 - cyanimino - imidazolidine and ammonium chloride according to Example 1. The dihydrochloride was obtained as an oil.

Oil bath temperature: 180°C; time: 1 hour.

Yield: 9% of theory.

Analysis:

Calculated:	C 31.60	H 6.63	N 30.70
Found:	31.90	6.54	30.70

Example 27

1 - Ethyl - 2 - (3 - butyl - guanidinylidene) - imidazolidine

Prepared from 1 - ethyl - 2 - cyanimino - imidazolidine and butylamine hydrochloride according to Example 1.

Oil bath temperature: 150—160°C; time: 15 minutes.

Yield: 23% of theory; melting point: 170°C (after recrystallization from isopropanol/ethyl acetate) (dihydrochloride).

Analysis:

Calculated:	C 42.26	H 8.16	N 24.64
Found:	42.30	7.46	24.60

Example 28

1 - Ethyl - 2 - [3 - (β - phenyl - ethyl) - guanidinylidene] - imidazolidine

Prepared from 1 - ethyl - 2 - cyanimino - imidazolidine and β - phenyl - ethylamine hydrochloride according to Example 1.

Yield: 62% of theory; melting point: 179°C (after recrystallization from isopropanol) (dihydrochloride).

Analysis:

Calculated:	C 50.60	H 6.98	N 21.08
Found:	50.90	7.06	21.00

Example 29

1 - (3,4 - Dichlorobenzyl) - 2 - [3 - (4 - chlorophenyl) - guanidinylidene] - imidazolidine

Prepared from 1 - (3,4 - dichlorobenzyl) - 2 - cyanimino - imidazolidine and *p* - chloro-

aniline hydrochloride according to Example 6.

Yield: 30% of theory; melting point: 171—173°C (hydrochloride).

Analysis:

Calculated:	C 47.18	H 3.96	N 16.16
Found:	47.40	3.78	16.20

Example 30

1 - Butyl - 2 - (3 - butyl - guanidinylidene - imidazolidine

Prepared from 1 - butyl - 2 - cyanimino - imidazolidine and butylamine hydrochloride according to Example 1.

Oil bath temperature: 150°C; time: 2 hours.

Yield: 65% of theory; melting point: 169—171°C (dihydrochloride).

Analysis:

Calculated:	C 46.18	H 8.72	N 22.40
Found:	46.25	8.58	22.25

Example 31

1 - (3,4 - Dichlorobenzyl) - 2 - [3 - (3,4 - dichlorobenzyl) - guanidinylidene] - imidazolidine

Prepared from 1 - (3,4 - dichlorobenzyl) - 2 - cyanimino - imidazolidine and 3,4 - dichlorobenzylamine hydrochloride according to Example 1. The hydrochloride was obtained as an oil.

Yield: 21% of theory.

Analysis:

Calculated:	C 44.85	H 3.76	N 14.54
Found:	44.75	3.98	14.55

Example 32

1 - Butyl - 2 - guanidinylidene - imidazolidine

Prepared from 1 - butyl - 2 - cyanimino - imidazolidine and ammonium chloride according to Example 1.

Oil bath temperature: 175°C; time: 2 hours.

Yield: 25% of theory; melting point: 164—165°C (after recrystallization from isopropanol) (dihydrochloride).

Analysis:

Calculated:	C 37.50	H 7.46	N 27.34
Found:	37.20	7.56	27.25

Example 33

1 - Butyl - 2 - [3 - (3,4 - dichlorobenzyl) - guanidinylidene] - imidazolidine

Prepared from 1 - butyl - 2 - cyanimino - imidazolidine and 3,4 - dichlorobenzylamine hydrochloride according to Example 7.

Oil bath temperature: 145°C; time: 1 hour.

Yield: 32% of theory; melting point: 170°C (hydrochloride).

Analysis:

Calculated:	C 47.60	H 5.85	N 18.50
Found:	47.65	5.85	18.60

Example 34

1 - Methyl - 2 - [3 - (4 - sulphanilamide) - guanidinylidene] - imidazolidine

3.99 g (23.16 mmol) of sulphanilamide and 2.88 g (23.2 mmol) of 1 - methyl - 2 - cyanimino - imidazolidine in a mixture of 10 ml of water and 2 ml of concentrated hydrochloric acid were refluxed for 4.5 hours. The solvent was then removed on a rotary evaporator and the residue was recrystallised twice from ethanol.

Yield: 41% of theory; melting point: 256—257°C (hydrochloride).

Analysis:

Calculated:	C 39.68	H 5.15	N 25.22
Found:	39.70	5.16	25.40

Example 35

1 - Phenyl - 2 - [3 - (3,4 - dichlorobenzyl) - guanidinylidene] - imidazolidene

Prepared from 1 - phenyl - 2 - cyanimino - imidazolidine and 3,4 - dichlorobenzylamine hydrochloride.

Oil bath temperature: 170°C; time: 15 minutes.

Isolation: The melt was recrystallised directly from ethanol/isopropanol.

Yield: 50% of theory; melting point: 201°C (hydrochloride).

Analysis:

Calculated:	C 51.20	H 4.55	N 17.57
Found:	51.10	4.51	17.65

Example 36

1 - Phenyl - 2 - [3 - (β - phenyl - ethyl) - guanidinylidene] - imidazolidine

Prepared from 1 - phenyl - 2 - cyanimino - imidazolidine and β - phenyl - ethylamine hydrochloride according to Example 1.

Yield: 10% of theory; melting point: 158°C (hydrochloride).

Analysis:

Calculated:	C 62.87	H 6.50	N 20.37
Found:	63.00	6.60	20.40

Example 37

1 - Ethyl - 2 - [3 - (3,4 - dichlorobenzyl) - guanidinylidene] - imidazolidine

Prepared from 1 - ethyl - 2 - cyanimino - imidazolidine and 3,4 - dichlorobenzylamine hydrochloride according to Example 1.

Oil bath temperature: 190°C; time: 15 minutes.

Yield: 72% of theory; melting point: 141°C (hydrochloride).

Analysis:

Calculated:

C 44.51 H 5.17 N 19.96 Cl 30.33

Found:

C 43.80 H 5.26 N 19.96 Cl 29.80

Example 38

1 - Methyl - 2 - [3 - (4 - carboxy - phenyl) - guanidinylidene] - imidazolidine

Prepared from 1 - methyl - 2 - cyanimino - imidazolidine and *p* - amino - benzoic acid hydrochloride according to Example 6.

Yield: 35% of theory; melting point: 271—272°C (after recrystallization from methanol) (hydrochloride).

Analysis:

Calculated:	C 48.50	H 5.43	N 23.53
Found:	48.70	5.42	23.58

Example 39

1 - (2 - Hydroxyethyl) - 2 - (3 - butyl - guanidinylidene) - imidazolidine

Prepared from 1 - (2 - hydroxyethyl) - 2 - cyanimino - imidazolidine and butylamine hydrochloride according to Example 1.

Yield: 8% of theory; melting point: 148—149°C (dihydrochloride).

Analysis:

Calculated:	C 40.02	H 7.72	N 23.33
Found:	39.85	7.70	23.40

Example 40

2 - (3 - Adamantyl - guanidinylidene - imidazolidine

Prepared from 2 - cyanimino - imidazolidine and adamantylamine hydrochloride according to Example 1.

Oil bath temperature: 210°C; time: 15 minutes.

Yield: 14% of theory; melting point: 230—232°C (dihydrochloride).

Analysis:

Calculated:	C 50.30	H 7.54	N 20.95
Found:	50.30	7.62	20.90

Example 41

1 - Methyl - 2 - [3 - (2 - hydroxyethyl) - guanidinylidene] - imidazolidine

Prepared from 1 - methyl - 2 - cyanimino - imidazolidine and ethanolamine hydrochloride according to Example 1.

Oil bath temperature: 150°C; time: 60 minutes.

Yield: 8% of theory; melting point: 154—155°C (dihydrochloride).

Analysis:

Calculated:	C 32.54	H 6.63	N 27.12
Found:	32.60	6.64	27.18

Example 42

4 - Methyl - 2 - [3 - (1 - methyl - propyl) - guanidinylidene] - imidazolidine

Prepared from 2 - cyanimino - 4 - methyl - imidazolidine and 2 - aminobutane hydrochloride according to Example 1.

Oil bath temperature: 150°C; time: 3.5 hours.

Yield: 11% of theory; melting point: 206—208°C (dihydrochloride).

Analysis:

Calculated:	C 40.04	H 7.82	N 25.91
Found:	39.80	8.32	25.82

Example 43

1 - Methyl - 2 - (3 - adamantyl - guanidinylidene) - imidazolidine

Prepared from 1 - methyl - 2 - cyanimino - imidazolidine and adamantylamine hydrochloride according to Example 1.

Oil bath temperature: 180—190°C; time: 20 minutes.

Yield: 7% of theory; melting point: 239°C (dihydrochloride).

Analysis:

Calculated:	C 57.76	H 8.40	N 22.46
Found:	57.30	8.65	22.20

Example 44

1 - (3,4 - Dichlorobenzyl) - 2 - (3 - adamantyl - guanidinylidene) - imidazolidine

Prepared from 1 - (3,4 - dichlorobenzyl) - 2 - cyanimino - imidazolidine and adamantylamine hydrochloride.

Oil bath temperature: 185°C; time: 20 minutes.

Isolation: Cooled melt recrystallised directly from methanol/water.

Yield: 11% of theory; melting point: 242°C (hydrochloride).

Analysis:

Calculated:

C 55.20 H 6.18 N 15.33 Cl 23.27

Found:

C 55.00 H 6.15 N 16.30 Cl 23.20

Example 45

1 - Phenyl - 2 - (3 - adamantyl - guanidinylidene) - imidazolidine

Prepared from 1 - phenyl - 2 - cyanimino - imidazolidine and adamantylamine hydrochloride.

Oil bath temperature: 180°C; time: 20 minutes.

Isolation: Melt crystallised directly from isopropanol.

Yield: 15% of theory; melting point: 255—256°C (hydrochloride).

Analysis:
Calculated:
C 64.26 H 7.55 N 9.48 Cl 18.74
Found:
C 63.70 H 7.64 N 10.25 Cl 18.70

Example 46

1 - Benzyl - 2 - guanidinylidene - imidazolidine

Prepared from 1 - benzyl - 2 - cyanimino - imidazolidine and ammonium chloride according to Example 1.

Oil bath temperature: 190—200°C; time: 30 minutes.

Yield: 8% of theory; melting point: 215—216°C (hydrochloride).

Analysis:
Calculated:
C 52.06 H 6.36 N 27.62 Cl 13.96
Found:
C 52.20 H 6.32 N 27.80 Cl 14.10

Example 47

1 - Phenyl - 2 - guanidinylidene - imidazolidine

Prepared from 1 - phenyl - 2 - cyanimino - imidazolidine and ammonium chloride according to Example 1.

Oil bath temperature: 190—200°C; time: 10 minutes.

Yield: 15% of theory; melting point: 242—243°C (hydrochloride).

Analysis:
Calculated:
C 50.12 H 5.89 N 29.22 Cl 14.77
Found:
C 50.50 H 5.99 N 29.15 Cl 14.75

Example 48

1 - Ethyl - 2 - guanidinylidene - hexahydropyrimidine

Prepared from 1 - ethyl - 2 - cyanimino - hexahydropyrimidine and ammonium chloride.

Oil bath temperature: 195°C; time: 25 minutes.

Isolation: Cooled melt recrystallised from isopropanol.

Yield: 24% of theory; melting point: 217°C (hydrochloride).

Analysis:
Calculated:
C 40.91 H 7.85 N 34.02 Cl 17.22
Found:
C 40.85 H 8.01 N 34.10 Cl 17.43

Example 49

1 - Butyl - 2 - (3 - butyl - guanidinylidene) - hexahydropyrimidine

Prepared from 1 - butyl - 2 - cyanimino - hexahydropyrimidine and butylamine hydrochloride.

Oil bath temperature: 180°C; time: 20 minutes.

Isolation: Cooled melt recrystallised from methyl ethyl ketone.

Yield: 5% of theory; melting point: 122°C (hydrochloride).

Analysis
Calculated:
C 53.85 H 9.73 N 24.18 Cl 12.23
Found:
C 53.70 H 9.77 N 24.05 Cl 12.10

Example 50

1 - Propyl - 2 - (3 - butyl - guanidinylidene) - hexahydropyrimidine

Prepared from 1 - propyl - 2 - cyanimino - hexahydropyrimidine and butylamine hydrochloride.

Oil bath temperature: 180°C; time: 15 minutes.

Isolation: Cooled melt recrystallised from ethyl acetate.

Yield: 58% of theory; melting point: 150°C (hydrochloride).

Analysis:
Calculated: C 52.25 H 9.50 N 25.40
Found: 52.00 9.33 25.45

Example 51

1 - Ethyl - 2 - (3 - butyl - guanidinylidene) - hexahydropyrimidine

Prepared from 1 - ethyl - 2 - cyanimino - hexahydropyrimidine and butylamine hydrochloride according to Example 50.

Yield: 53% of theory; melting point: 135°C (hydrochloride).

Analysis:
Calculated: C 50.48 H 9.24 N 26.76
Found: 50.50 9.16 26.60

Example 52

1 - Butyl - 2 - guanidinylidene - hexahydropyrimidine

Prepared from 1 - butyl - 2 - cyanimino - hexahydropyrimidine and ammonium chloride according to Example 48.

Yield: 34% of theory; melting point: 200—202°C (hydrochloride).

Analysis:
Calculated:
C 46.21 H 8.62 N 29.98 Cl 15.19
Found:
C 45.90 H 8.76 N 30.50 Cl 15.81

Example 53

1 - Propyl - 2 - guanidinylidene - hexahydropyrimidine

Prepared from 1 - propyl - 2 - cyanimino - hexahydropyrimidine and ammonium chloride according to Example 48.

Yield: 30% of theory; melting point: 212°C (hydrochloride).

Analysis:
Calculated:
C 43.72 H 8.28 N 31.84 Cl 16.16
Found:
C 43.80 H 8.45 N 31.80 Cl 16.62

Example 54

1 - Methyl - 2 - (3 - butyl - guanidinylidene) - hexahydropyrimidine

Prepared from 1 - methyl - 2 - cyanimino - hexahydro - pyrimidine and butylamine hydrochloride according to Example 50.

Yield: 52% of theory; melting point: 189—190°C (after recrystallization from methyl ethyl ketone/isopropanol) (hydrochloride).

Analysis:

Calculated:	C 48.48	H 8.95	N 28.27
Found:	48.50	8.88	28.05

Example 55

2 - (3 - Butyl - guanidinylidene) - 4 - methyl - imidazolidine

Prepared from 2 - cyanimino - 4 - methyl - imidazolidine and butylamine hydrochloride according to Example 42.

Yield: 4% of theory; melting point: 203—204°C (dihydrochloride).

Analysis:

Calculated:	C 40.00	H 7.83	N 25.91
Found:	39.80	7.98	25.90

Example 56

2 - [3 - (β - Phenyl - ethyl) - guanidinylidene] - 4 - methyl - imidazolidine

Prepared from 2 - cyanimino - 4 - methyl - imidazolidine and β - phenyl - ethylamine hydrochloride according to Example 42.

Yield: 9% of theory; melting point: 207—208°C (dihydrochloride).

Analysis:

Calculated:	C 49.10	H 6.65	N 21.98
Found:	49.20	6.63	22.10

Example 57

1 - Methyl - 2 - guanidinylidene - hexahydropyrimidine

Prepared from 1 - methyl - 2 - cyanimino - hexahydropyrimidine and ammonium chloride according to Example 48.

Yield: 5% of theory; melting point: 235—237°C (hydrochloride).

Analysis:
Calculated:
C 37.55 H 7.36 N 36.95 Cl 18.57
Found:
C 37.60 H 7.43 N 35.90 Cl 18.10

Example 58

2 - [3 - (2 - (4 - Chlorophenyl) - ethyl) - guanidinylidene] - imidazolidine

Prepared from 2 - cyanimino - imidazolidine and 2 - (4 - chlorophenyl) - ethylamine hydrochloride according to Example 1.

Oil bath temperature: 180°C; time: 10 minutes.

Yield: 16% of theory; melting point: decomposition at 230°C (dihydrochloride).

Analysis:

Calculated:	C 42.55	H 5.35	N 20.68
Found:	42.40	5.48	20.70

Example 59

2 - [3 - (2 - (4 - Methyl - phenyl) - ethyl) - guanidinylidene] - imidazolidine

Prepared from 2 - cyanimino - imidazolidine and 2 - (4 - methyl - phenyl) - ethylamine hydrochloride according to Example 58.

Yield: 28% of theory; melting point: 204—205°C (dihydrochloride).

Analysis:

Calculated:	C 49.00	H 6.65	N 22.00
Found:	49.10	6.75	22.45

Example 60

1 - (p - Chlorophenyl) - 2 - [3 - (3,4 - dichlorobenzyl) - guanidinylidene] - imidazolidine

Prepared from 1 - (p - chlorophenyl) - 2 - cyanimino - imidazolidine and 3,4 - dichlorobenzylamine hydrochloride.

Oil bath temperature: 190°C; time: 15 minutes.

Isolation: Melt recrystallised from methyl ethyl ketone.

Yield: 69% of theory; melting point: 171°C (hydrochloride).

Analysis:

Calculated:	C 47.13	H 3.96	Cl 32.74
Found:	47.10	3.97	32.85

Example 61

2 - [3 - (2 - (4 - Methoxy - phenyl) - ethyl) - guanidinylidene] - imidazolidine

Prepared from 2 - cyanimino - imidazolidine and 2 - (4 - methoxy - phenyl) - ethylamine hydrochloride according to Example 58.

Yield: 27% of theory; melting point: 198—200°C (dihydrochloride).

Analysis:

Calculated:	C 46.74	H 6.33	N 20.97
Found:	46.80	6.35	21.25

Example 62

2 - (2 - Butyl - guanidinylidene) - 4,4 - dimethyl - imidazolidine

Prepared from 2 - cyanimino - 4,4 - di-

methyl - imidazolidine and butylamine hydrochloride according to Example 1.

Yield: 28% of theory; melting point: 208°C (dihydrochloride).

Analysis:

Calculated:	C 42.25	H 8.15	N 24.64
Found:	42.30	8.34	24.85

Example 63

2 - [3 - (β - phenyl - ethyl) - guanidinylidene] - hexahydropyrimidine

Prepared from 2 - cyanimino - hexahydropyrimidine and β - phenyl - ethylamine hydrochloride according to Example 50.

Yield: 18% of theory; melting point: 152—154°C (after recrystallization from isopropanol) (hydrochloride).

Analysis:

Calculated:

C 55.41 H 7.15 N 24.85 Cl 12.59

Found:

C 55.70 H 7.11 N 24.82 Cl 12.71

Example 64

2 - Guanidinylidene - hexahydropyrimidine

Prepared from 2 - cyanimino - hexahydropyrimidine and ammonium chloride.

Oil bath temperature: 210°C; time 15 minutes.

Yield: 6% of theory; melting point: 237—240°C (hydrochloride).

Analysis:

Calculated:

C 33.89 H 6.80 N 39.50 Cl 20.00

Found:

C 33.85 H 6.77 N 39.15 Cl 20.12

Example 65

2 - [3 - (β - Phenyl - ethyl) - guanidinylidene] - 4,4 - dimethylimidazolidine

Prepared from 2 - cyanimino - 4,4 - dimethyl - imidazolidine and β - phenyl - ethylamine hydrochloride according to Example 1.

Yield: 35% of theory; melting point: 202°C (dihydrochloride).

Analysis:

Calculated:	C 50.50	H 6.97	N 21.08	
Found:	50.80	7.10	20.78	

Example 66

1 - Methyl - 2 - [3 - (2,6 - dichlorophenyl) - guanidinylidene] - imidazolidine

Prepared from 1 - methyl - 2 - cyanimino - imidazolidine and 2,6 - dichloroaniline hydrochloride.

Oil bath temperature: 160°C; time: 20 minutes.

Isolation: Cooled melt recrystallised from isopropanol:

Yield: 50% of theory; melting point: 233°C (hydrochloride).

Analysis:

Calculated:	C 40.90	H 4.37	N 21.71	
Found:	41.00	4.32	21.50	

Example 67

2 - [3 - (2,6 - Dichlorophenyl) - guanidinylidene] - imidazolidine

Prepared from 2 - cyanimino - imidazolidine and 2,6 - dichloroaniline hydrochloride.

Oil bath temperature: 160°C; time 20 minutes.

Isolation: Cooled melt boiled with isopropanol and diethyl ether then added.

Yield: 3.3% of theory; melting point: 229°C (after recrystallization from isopropanol) (hydrochloride).

Analysis:

Calculated:	C 38.90	H 3.91	N 22.69	
Found:	38.80	3.92	22.85	

Example 68

1 - Butyl - 2 - guanidinylidene - 5,5 - dimethyl - imidazolidine

Prepared from 1 - butyl - 2 - cyanimino - 5,5 - dimethyl - imidazolidine and ammonium chloride according to Example 1.

Yield: 14% of theory; melting point: 137—138°C (dihydrochloride).

Analysis:

Calculated:	C 42.25	H 8.15	N 24.64
Found:	42.50	8.32	24.81

Example 69

1 - (4 - Chlorophenyl) - 2 - (3 - adamantyl - guanidinylidene) - imidazolidine

Prepared from 1 - (4 - chlorophenyl) - 2 - cyanimino - imidazolidine and adamantylamine hydrochloride.

Oil bath temperature: 210°C; time: 20 minutes.

Isolation: Melt dissolved in hot methanol, 1/10 N hydrochloric acid added until solution become cloudy and the solution then left to crystallise.

Yield: 24% of theory; melting point: 275°C (after recrystallization from water) (hydrochloride).

Analysis:

Calculated:

C 58.82 H 6.66 N 17.15 Cl 17.36

Found:

C 57.90 H 6.97 N 17.35 Cl 17.45

Example 70

2 - (3 - Methyl - guanidinylidene) - 4 - methyl - imidazolidine

Prepared from 2 - cyanimino - 4 - methyl - imidazolidine and methylamine hydrochloride according to Example 1.

Oil bath temperature: 180°C; time: 25 minutes.

Yield: 3% of theory; melting point: 212—214°C (dihydrochloride).

Analysis:
Calculated:
C 31.58 H 6.63 N 30.70 Cl 31.09
Found:
C 31.65 H 6.64 N 30.15 Cl 31.35

Example 71

2 - (3,3 - Dimethyl - guanidinylidene) - 4 - methyl - imidazolidine

Prepared from 2 - cyanimino - 4 - methyl - imidazolidine and dimethylamine hydrochloride according to Example 1.

Oil bath temperature: 180°C; melting point: 215—217°C (after recrystallization from isopropanol) (dihydrochloride).

Analysis:
Calculated:
C 34.72 H 7.08 N 28.92 Cl 29.28
Found:
C 34.25 H 7.12 N 28.65 Cl 28.62

Example 72

1 - (β - Phenyl - ethyl) - 2 - (3 - butyl - guanidinylidene) - hexahydropyrimidine

Prepared from 1 - (β - phenyl - ethyl) - 2 - cyanimino - hexahydropyrimidine and butylamine hydrochloride according to Example 50.

Yield: 20% of theory; melting point: 161—163°C (hydrochloride).

Analysis:
Calculated:
C 60.43 H 8.35 N 20.73 Cl 10.49
Found:
C 60.60 H 8.50 N 20.60 Cl 10.57

Example 73

2 - (3 - Benzyl - guanidinylidene) - hexahydropyrimidine

Prepared from 2 - cyanimino - hexahydropyrimidine and benzylamine hydrochloride according to Example 50.

Yield: 32% of theory; melting point: 170—172°C (after recrystallization from isopropanol) (hydrochloride).

Analysis:
Calculated:
C 53.83 H 6.78 N 26.15 Cl 13.24
Found:
C 53.95 H 6.87 N 26.15 Cl 13.23

Example 74

2 - (3 - Propyl - guanidinylidene) - 4 - methyl - imidazolidine

Prepared from 2 - cyanimino - 4 - methyl - imidazolidine and propylamine hydrochloride according to Example 1.

Oil bath temperature: 180°C; time: 30 minutes.

Yield: 10% of theory; melting point: 218—220°C (after recrystallization from isopropanol) (dihydrochloride).

Analysis:
Calculated:
C 37.51 H 7.48 N 27.33 Cl 27.68
Found:
C 37.75 H 7.52 N 27.25 Cl 27.50

Example 75

1 - (β - Phenyl - ethyl) - 2 - guanidinylidene - hexahydropyrimidine

Prepared from 1 - (β - phenyl - ethyl) - 2 - cyanimino - hexahydropyrimidine and ammonium chloride.

Oil bath temperature: 210°C; time: 30 minutes.

Isolation: Cooled melt was recrystallised directly from isopropanol.

Yield: 18% of theory; melting point: 220—221°C (hydrochloride).

Analysis:
Calculated:
C 55.41 H 7.16 N 24.85 Cl 12.58
Found:
C 55.30 H 7.16 N 24.75 Cl 12.72

Example 76

1 - (β - Phenyl - ethyl) - 2 - (3 - propyl - guanidinylidene) - hexahydropyrimidine

Prepared from 1 - (β - phenyl - ethyl) - 2 - cyanimino - hexahydropyrimidine and propylamine hydrochloride according to Example 50.

Yield: 28% of theory; melting point: 187—188°C (after recrystallization from methyl ethyl ketone) (hydrochloride).

Analysis:
Calculated:
C 59.34 H 8.09 N 21.62 Cl 10.95
Found:
C 59.60 H 8.15 N 21.50 Cl 10.98

Example 77

1 - (β - Phenyl - ethyl) - 2 - [3 - (β - phenyl - ethyl) - guanidinylidene] - hexahydropyrimidine

Prepared from 1 - (β - phenyl - ethyl) - 2 - cyanimino - hexahydropyrimidine and β - phenyl - ethylamine hydrochloride according to Example 50.

Yield: 50% of theory; melting point: 170—171°C (hydrochloride).

Analysis:
Calculated:
C 65.35 H 7.31 N 18.15 Cl 9.19
Found:
C 65.30 H 7.39 N 18.10 Cl 9.18

Example 78

1 - Phenyl - 2 - (3 - isopropyl - guanidinylidene) - imidazolidine

Prepared from 1 - phenyl - 2 - cyanimino - imidazolidine and isopropylamine hydrochloride according to Example 1.

Yield: 5% of theory; melting point: 194—196°C (hydrochloride).

Analysis:
Calculated:
C 55.41 H 7.15 N 24.86 Cl 12.58
Found:
C 55.30 H 7.14 N 24.75 Cl 12.68

Example 79

1 - Butyl - 2 - [3 - (β - phenyl - ethyl) - guanidinylidene] - hexahydropyrimidine

Prepared from 1 - butyl - 2 - cyanimino - hexahydropyrimidine and β - phenyl - ethylamine hydrochloride according to Example 50.

Yield: 9% of theory; melting point: 165—167°C (hydrochloride).

Analysis:
Calculated:
C 60.44 H 8.35 N 20.72 Cl 10.49
Found:
C 60.20 H 8.27 N 20.80 Cl 10.60

Example 80

1 - Ethyl - 2 - (3 - isobutyl - guanidinylidene) - imidazolidine

Prepared from 1 - ethyl - 2 - cyanimino - imidazolidene and isobutylamine hydrochloride according to Example 1.

Yield: 4.5% of theory; melting point: 180—182°C (after recrystallization from isopropanol) (dihydrochloride).

Analysis:
Calculated:
C 42.26 H 8.16 N 24.64 Cl 29.94
Found:
C 42.55 H 8.20 N 24.60 Cl 24.85

Example 81

1 - Ethyl - 2 - [3 - (1 - methyl - propyl) - guanidinylidene] - imidiazoline

Prepared from 1 - ethyl - 2 - cyanimino - imidazolidine and 2 - aminobutane hydrochloride according to Example 1.

Yield: 28% of theory; melting point: 168—170°C (after recrystallization from isopropanol/ethyl acetate) (dihydrochloride).

Analysis:
Calculated:
C 42.26 H 8.16 N 24.64 Cl 24.94
Found:
C 42.45 H 8.32 N 24.40 Cl 23.70

Example 82

1 - (4 - Methyl - phenyl) - 2 - (3 - isobutyl - guanidinylidene) - imidazolidine

Prepared from 1 - (4 - methyl - phenyl) - 2 - cyanimino - imidazolidine and isobutylamine hydrochloride according to Example 1.

Yield: 19% of theory; melting point: 203—204°C (after recrystallization from water) (hydrochloride).

Analysis:
Calculated:
C 58.15 H 7.81 N 22.60 Cl 11.44
Found:
C 58.50 H 7.91 N 22.65 Cl 11.30

Example 83

2 - (3 - Isobutyl - guanidinylidene) - imidazolidine

Prepared from 2 - cyanimino - imidazolidine and isobutylamine hydrochloride according to Example 1.

Yield: 18% of theory; melting point: 217°C (after recrystallization from isopropanol) (dihydrochloride).

Analysis:
Calculated:
C 37.51 H 7.47 N 27.34 Cl 27.68
Found:
C 37.80 H 7.62 N 27.50 Cl 27.55

Example 84

1 - (4 - Methyl - phenyl - 2 - (3 - propyl - guanidinylidene) - imidazolidine

Prepared from 1 - (4 - Methyl - phenyl) - 2 - cyanimino - imidazolidine and propylamine hydrochloride.

Oil bath temperature: 180°C; time: 40 minutes.

Isolation: Cooled melt recrystallised directly from acetone.

Yield: 22% of theory; melting point: 180—182°C (hydrochloride).

Analysis:
Calculated:
C 56.85 H 7.49 N 23.67 Cl 11.99
Found:
C 57.00 H 7.81 N 23.75 Cl 12.03

Example 85

1 - (4 - Methyl - phenyl) - 2 - (3 - butyl - guanidinylidene) - imidazolidine

Prepared from 1 - (4 - methyl - phenyl) - 2 - cyanimino - imidazolidine and butylamine hydrochloride according to Example 84.

Oil bath temperature: 190°C; time: 35 minutes.

Yield: 26% of theory; melting point: 156—157°C (hydrochloride).

Analysis:
Calculated:
C 58.15 H 7.81 N 22.60 Cl 11.44
Found:
C 58.30 H 8.03 N 22.50 Cl 11.25

Example 86

2 - [3 - (β - Phenyl - ethyl) - guanidinylidene] - 5 - methyl - hexahydropyrimidine

Prepared from 2 - cyanimino - 5 - methyl - hexahydropyrimidine and β - phenyl - ethylamine hydrochloride.

Oil bath temperature: 155°C; time: 20 minutes.

Isolation: Cooled melt recrystallised directly from isopropanol.

Yield: 56% of theory; melting point: 180—181°C (hydrochloride).

Analysis:
Calculated: C 56.85 H 7.50 N 23.72
Found: 57.00 7.38 23.70

Example 87

2 - [3 - (β - Phenyl - ethyl) - guanidinylidene] - 5,5 - dimethyl - hexahydropyrimidine

Prepared from 2 - cyanimino - 5,5 - dimethyl - hexahydropyrimidine and β - phenyl - ethylamine hydrochloride according to Example 86.

Yield: 56% of theory; melting point: 125—130°C (hydrochloride).

Analysis:
Calculated: C 58.20 H 7.80 N 22.00
Found: 58.50 7.74 22.65

Example 88

2 - (3 - Isobutyl - guanidinylidene) - 5 - methyl - hexahydropyrimidine

Prepared from 2 - cyanimino - 5 - methyl - hexahydropyrimidine and isobutylamine hydrochloride according to Example 86.

Yield: 56% of theory; melting point: 146—147°C (hydrochloride).

Analysis:
Calculated: C 48.50 H 8.95 N 28.26
Found: 48.70 9.00 28.00

Example 89

1 - Ethyl - 2 - (3 - t - butyl - guanidinylidene) - imidazolidine

Prepared from 1 - ethyl - 2 - cyanimino - imidazolidine and t - butylamine hydrochloride according to Example 1.

Yield: 7% of theory; melting point: 170°C (after recrystallization from isopropanol/ethyl acetate) (dihydrochloride).

Analysis:
Calculated:
C 42.26 H 8.16 N 24.64 Cl 24.94
Found:
C 42.00 H 8.29 N 24.50 Cl 24.60

Example 90

1 - Methyl - 2 - (3 - isobutyl - guanidinylidene) - imidazolidine

Prepared from 1 - methyl - 2 - cyanimino - imidazolidine and isobutylamine hydrochloride according to Example 1.

Yield: 18% of theory; melting point: 190—191°C (after recrystallization from isopropanol) (dihydrochloride).

Analysis:
Calculated:
C 40.01 H 7.83 N 25.92 Cl 26.24
Found:
C 40.00 H 7.94 N 25.90 Cl 26.00

Example 91

1 - (β - Phenyl - ethyl) - 2 - (3 - isobutyl - guanidinylidene) - imidazolidine

Prepared from 1 - (β - phenyl - ethyl) - 2 - cyanimino - imidazolidine and isobutylamine hydrochloride.

Oil bath temperature: 150°C; time: 40 minutes.

Isolation: Cooled melt recrystallised directly from ethyl acetate.

Yield: 9% of theory; melting point: 180°C (dihydrochloride).

Analysis:
Calculated:
C 53.33 H 7.55 N 19.44 Cl 19.68
Found:
C 53.50 H 7.61 N 19.00 Cl 19.50

Example 92

1 - (4 - Methoxy - phenyl) - 2 - (3 - isobutyl - guanidinylidene) - imidazolidine

Prepared from 1 - (4 - methoxy - phenyl) - 2 - cyanimino - imidazolidine and isobutylamine hydrochloride.

Oil bath temperature: 190°C; time: 30 minutes.

Isolation: Cooled melt recrystallised directly from acetone.

Yield: 31% of theory; melting point: 187°C (after recrystallization from water) (hydrochloride).

Analysis:
Calculated:
C 55.30 H 7.42 N 21.49 Cl 10.88
Found:
C 55.15 H 7.61 N 21.35 Cl 10.80

Example 93

1 - (4 - Methoxy - phenyl) - 2 - (3 - butyl - guanidinylidene) - imidazolidine

Prepared from 1 - (4 - methoxy - phenyl) -

2 - cyanimino - imidazolidine and butylamine hydrochloride analogously to Example 92.

Yield: 34% of theory; melting point: 115—116°C (after recrystallization from water) (hydrochloride).

Analysis:
Calculated:
C 55.30 H 7.42 N 21.49 Cl 10.88
Found:
C 55.50 H 7.32 N 21.35 Cl 10.72

Example 94

1 - Ethyl - 2 - (3 - isobutyl - guanidinylidene) - hexahydropyrimidine

Prepared from 1 - ethyl - 2 - cyanimino - hexahydropyrimidine and isobutylamine hydrochloride.

Oil bath temperature: 180°C; time: 15 minutes.

Isolation: Cooled melt recrystallized directly from ethyl acetate/isopropanol.

Yield: 55% of theory; melting point: 200°C (hydrochloride).

Analysis:
Calculated:
C 50.47 H 9.24 N 26.75 Cl 13.54
Found:
C 50.25 H 9.40 N 26.52 Cl 13.37

Example 95

1 - (4 - Methoxy - phenyl) - 2 - (3 - propyl - guanidinylidene) - imidazolidine

Prepared from 1 - (4 - methoxy - phenyl) - 2 - cyanimino - imidazolidine and propylamine hydrochloride analogously to Example 92.

Yield: 28% of theory; melting point: 123—125°C (hydrochloride).

Analysis:
Calculated:
C 53.94 H 7.11 N 22.46 Cl 11.37
Found:
C 54.10 H 7.04 N 2.95 Cl 11.25

Example 96

1 - Butyl - 2 - (3 - hexyl - guanidinylidene) - imidazolidine

Prepared from 1 - butyl - 2 - cyanimino - imidazolidine and hexylamine hydrochloride according to Example 1.

Yield: 38.5% of theory; melting point: 130°C (hydrochloride).

Analysis:
Calculated: C 49.41 H 9.18 N 20.58
Found: 49.80 9.28 20.05

Example 97

1 - (3 - Methoxy - phenyl) - 2 - [3 - (2 - methyl - propyl) - guanidinylidene] - imidazolidine

Prepared from 1 - (3 - methoxy - phenyl) - 2 - cyanimino - imidazolidine and isobutylamine hydrochloride according to Example 92.

Yield: 46% of theory; melting point: 174°C (hydrochloride).

Analysis:
Calculated:
C 55.30 H 7.42 N 21.49 Cl 10.88
Found:
C 55.40 H 7.51 N 21.68 Cl 10.70

Example 98

1 - (3 - Methoxy - phenyl) - 2 - (3 - butyl - guanidinylidene) - imidazolidine

Prepared from 1 - (3 - methoxy - phenyl) - 2 - cyanimino - imidazolidine and butylamine hydrochloride according to Example 92.

Yield: 38% of theory; melting point: 72—73°C (hydrochloride).

Analysis:
Calculated:
C 55.30 H 7.42 N 21.49 Cl 10.88
Found:
C 55.40 H 7.51 N 21.68 Cl 10.70

Example 99

1 - (3 - Methoxy - phenyl) - 2 - (3 - propyl - guanidinylidene) - imidazolidine

Prepared from 1 - (3 - methoxy - phenyl) - 2 - cyanimino - imidazolidine and propylamine hydrochloride according to Example 92.

Yield: 42% of theory; melting point: 131°C (hydrochloride).

Analysis:
Calculated:
C 53.94 H 7.11 N 22.46 Cl 11.37
Found:
C 53.60 H 6.98 N 22.60 Cl 11.12

Example 100

1 - Butyl - 2 - (3 - isobutyl - guanidinylidene) - imidazolidine

Prepared from 1 - butyl - 2 - cyanimino - imidazolidine and isobutylamine hydrochloride according to Example 1.

Yield: 44.8% of theory; melting point: 205—206°C (dihydrochloride).

Analysis:
Calculated:
C 46.16 H 8.71 N 22.43 Cl 22.70
Found:
C 46.40 H 8.55 N 22.65 Cl 22.60

Example 101

1 - Isobutyl - 2 - (3 - isobutyl - guanidinylidene) - imidazolidine

Prepared from 1 - isobutyl - 2 - cyanimino - imidazolidine and isobutylamine hydrochloride according to Example 1.

Yield: 33.3% of theory; melting point: 184—185°C (dihydrochloride).

Analysis:
Calculated:
C 46.16 H 8.71 N 22.43 Cl 22.70
Found:
C 46.30 H 8.67 N 22.20 Cl 22.60

Example 102

1 - Isobutyl - 2 - [3 - (β - phenyl - ethyl) - guanidinylidene] - imidazolidine

Prepared from 1 - isobutyl - 2 - cyanimino - imidazolidine and β - phenyl - ethylamine hydrochloride according to Example 1.

Yield: 47.5% of theory; melting point: 153—155°C (hydrochloride).

Analysis:
Calculated: C 53.34 H 7.55 N 19.43
Found: 53.30 7.64 19.00

Example 103

1 - Isobutyl - 2 - guanidinylidene - imidazolidine

Prepared from 1 - isobutyl - 2 - cyanimino - imidazolidine and ammonium chloride according to Example 1.

Yield: 37.9% of theory; melting point: 223°C (dihydrochloride).

Analysis:
Calculated:
C 37.51 H 7.47 N 27.34 Cl 27.68
Found:
C 37.60 H 7.36 N 27.50 Cl 27.80

Example 104

1 - Methyl - 2 - [3 - (β - phenyl - ethyl) - guanidinylidene] - imidazolidine

a) 1 - Methyl - 2 - thiocarbamoylimino - imidazolidine

A solution of 24.8 g (0.2 mol) of 2 - cyanimino - 1 - methyl - imidazolidine in 160 ml of absolute ethanol to which 1.5 g (0.01 mol) of triethanolamine had been added was saturated with hydrogen sulphide in an autoclave and heated to 50°C for 8 hours. After cooling and blowing out any remaining hydrogen sulphide, the precipitate was separated by filtration at the pump and washed with absolute ethanol and absolute ether. The dried product was sufficiently pure for use in subsequent reactions.

Yield: 27.4 g (87% of theory); melting point: 151—152°C, pale yellow crystals.

A sample was recrystallised from absolute ethanol for analysis:

M.p.: 150—152°C.

$C_5H_{10}N_4S$ (158.2)
Calculated:
C 37.97 H 6.37 N 35.42 S 20.23
Found:
C 37.90 H 6.31 N 35.50 S 20.45

UV absorption (ethanol): 246 μ (0.90) and 282 μ (0.75).

UV absorption after the addition of potassium hydroxide solution: 246 μ (1.05) and 282 μ (0.92).

The yield obtained in the preparation of a further batch from 0.6 mol of starting material was 89.5 g (94% of theory).

b) S - Methyl - 1 - (1 - methyl - 2 - imidazolin - 2 - yl) - thiourea hydriodide

A mixture of 84.5 g (0.535 mol) of 1 - methyl - 2 - thiocarbamoyl - imino - imidazolidine, 70 ml of absolute ethanol and 77 g (33.7 ml) of methyl iodide (0.543 mol) was heated under reflux on a steam bath for 45 minutes. After cooling, the reaction mixture was clarified by filtering it through a frit coated with "Celite" (registered Trade Mark). Absolute ether was then added until the filtrate remained cloudy and the filtrate was then seeded to effect crystallisation. The pale yellow crystals which separated were isolated by filtration at the pump, washed with ether/ethanol (10:1) and dried. Yield: 118.7 g (74% of theory); m.p.: 122—125°C (decomposition). A sample was recrystallised from ethanol (+ether) for analysis.

$C_6H_{13}IN_4S$ (300.2)
Calculated: C 24.00 H 4.37 N 18.67
Found: 24.15 4.36 18.70

Another batch was prepared from 0.139 mol of starting material in a yield of 89% of theory.

c) 1 - Methyl - 2 - [3 - (β - phenyl - ethyl) - guanidinylidene] - imidazolidine

300 mg of S - methyl - 1 - (1 - methyl - 2 - imidazolin - 2 - yl) - thiourea hydriodide (1 mmol) were dissolved in 10 ml of absolute ethanol, and 121 mg (1 mmol) of absolute β - phenyl - ethylamine were added. The reaction mixture was then heated to 75°C on a water bath for 20 minutes. Vigorous evolution of mercaptan occurred immediately. The reaction mixture was concentrated by evaporation and then cooled. The crystal paste thus obtained was isolated by filtration at the pump and recrystallised from ethanol. M.p.: 160°C (dihydrochloride).

The following Examples I to V illustrate the preparation of pharmaceutical compositions according to the present invention:

Example I

Tincture containing 1 - (3,4 - dichlorobenzyl) - 2 - (3 - adamantyl - guanidinylidene) - imidazolidine as active ingredient

Composition:
100 g contained:

1 - (3,4 - dichlorobenzyl) - 2 - (3 - adamantyl - guanidinylidene) - imidazolidine	2.0 g
Distilled water	50.0 g
Isopropanol	ad 100.0 g

Method of preparation:
The active substance was dissolved in distilled water and made up to the required volume with isopropanol.

Example II

Ointment containing 1 - (3,4 - dichlorobenzyl) - 2 - (3 - adamantyl - guanidinylidene) - imidazolidine as active ingredient

Composition:
100 g contain:

1 - (3,4 - dichlorobenzyl) - 2 - (3 - adamantyl - guanidinylidene) imidazolidine	2.0 g
Dehymuls K (registered Trade Mark)	60.0 g
Distilled water	38.0 g

(Dehymuls K is a high molecular weight aliphatic mixed ester which contains small quantities of hydrocarbons and "Cetiol"; "Cetiol" is a registered Trade Mark).

Method of preparation:
The active substance was dissolved in water heated to 70°C, the Dehymuls K was melted at 70°C and the two phases were emulsified together and cooled with stirring.

Example III

Tablets containing 50 mg of 1 - methyl - 2 - guanidinylidene - imidazolidine as active ingredient

Composition:
1 Tablet contains:

1 - methyl - 2 - guanidinylidene - imidazolidine	50.0 mg
Lactose	70.0 mg
Corn Starch	74.0 mg
Polyvinyl pyrrolidone	5.0 mg
Microcrystalline cellulose	20.0 mg
Magnesium stearate	1.0 mg
	220.0 mg

Method of preparation:
The active ingredient, lactose and corn starch were mixed together and moistened with a 15% alcoholic solution of polyvinyl pyrrolidone. The moist mixture was granulated through a 1.5 mm mesh sieve, dried at 45°C and again passed through the 1.5 mm mesh sieve. Microcrystalline cellulose and magnesium stearate were then added and the mixture was made homogeneous in a cubical mixer. The substance was pressed into tablets using a conventional tablet press.

Weight of tablet:	220 mg
Punch:	9 mm

Example IV

Dragées containing 75 mg of active ingredient

1 dragée contains:

1 - ethyl - 2 - (3 - butyl - guanidinylidene) - imidazolidine	75.0 mg
Polyvinyl acetate	30.0 mg
Carboxymethylcellulose	144.0 mg
Magnesium stearate	1.0 mg
	250.0 mg

Method of Preparation
The active ingredient and carboxymethyl cellulose were mixed together and then vigorously kneaded with a solution of polyvinyl acetate in acetone. When the substance had been uniformly moistened, it was passed through a sieve with a 1.5 mm mesh dried at 45°C and then again passed through the 1.5 mm mesh sieve. Magnesium stearate was added and the mixture was made homogeneous. The mixture was pressed into dragée cores using a conventional tablet press.

Weight of dragée cores:	250 mg
Punch:	9 mm.

Dragée cores prepared as described above were coated in known manner with a coating which consisted mainly of sugar and talcum. The coated dragées were then polished with beeswax.

Weight of dragée: 350 mg.

Example V

Cream containing 1 - (3,4 - dichlorobenzyl) - 2 - (3 - adamantyl - guanidinylidene) - imidazolidine as active ingredient

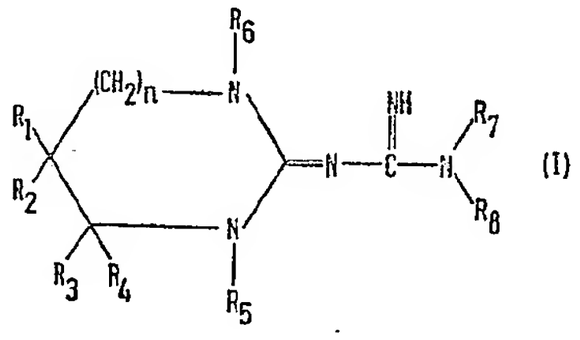
Composition:
100 g contain:

1 - (3,4 - dichlorobenzyl) - 2 - (3 - adamantyl - guanidinylidene) - imidazolidine	2.0 g
"Cremophor" A (registered Trade Mark)	4.0 g
Glycerol monostearate	4.0 g
Cetyl alcohol	8.0 g
Isopropyl myristate	10.0 g
Distilled water	72.0 g

Method of preparation:
The active substance was dissolved in water heated to a temperature of about 70°C. Cremophor A, glycerol monostearate, cetyl alcohol and isopropyl myristate were fused together at 70°C. The two phases were combined to produce an emulsion which was cooled with stirring.

WHAT WE CLAIM IS:—

1. Compounds of the general formula:—



(I)

[wherein R_1 and R_2, which may be the same or different, represent hydrogen atoms or straight chain or branched chain alkyl groups containing from 1 to 4 carbon atoms, or one of the groups R_1 and R_2 represents a hydroxyl group, and the other of the groups R_1 and R_2 is as hereinbefore defined;

R_3 and R_4, which may be the same or different, represent hydrogen atoms or straight chain or branched chain alkyl groups containing from 1 to 4 carbon atoms;

R_5 represents a hydrogen atom, a straight chain or branched chain alkyl group containing from 1 to 6 carbon atoms, a hydroxyalkyl group containing 2 or 3 carbon atoms, a phenyl group optionally mono- or di-substituted by alkyl or alkoxy groups containing 1 or 2 carbon atoms or by fluorine, chlorine or bromine atoms or by nitrile groups, a benzyl or phenylethyl group optionally mono- or di-substituted by halogen atoms, or an adamantyl group;

R_6 represents a hydrogen atom or a straight chain or branched chain alkyl group containing from 1 to 4 carbon atoms;

R_7 represents a hydrogen atom, a straight chain or branched chain alkyl group containing from 1 to 6 carbon atoms, a hydroxyalkyl group containing 2 or 3 carbon atoms, a benzyl or phenylethyl group optionally substituted by halogen atoms or by alkyl or alkoxy groups containing 1 or 2 carbon atoms, a phenyl group optionally substituted by chlorine atoms, carboxyl groups or aminosulphonyl groups, or an adamantyl group; and

R_8 represents a hydrogen atom or a straight chain or branched chain alkyl group containing from 1 to 4 carbon atoms; or

R_7 together with R_8 and the nitrogen atom to which they are attached represent a 5-, 6- or 7-membered saturated heterocyclic ring which may if desired be interrupted by an oxygen or sulphur atom or by another nitrogen atom which in turn may optionally be substituted by an alkyl group containing from 1 to 3 carbon atoms or by a phenyl group; and

n=0 or 1],

and acid addition salts thereof.

2. 2 - [3 - (β - Phenylethyl) - guanidinylidene] - imidazolidine and physiologically acceptable acid addition salts thereof.

3. 1 - Methyl - 2 - [3 - (β - phenylethyl) - guanidinylidene] - imidazolidine and physiologically acceptable acid addition salts thereof.

4. 2 - (3 - Butyl - guanidinylidene) - imidazolidine and physiologically acceptable acid addition salts thereof.

5. 1 - (β - Phenylethyl) - 2 - guanidinylidene - imidazolidine and physiologically acceptable acid addition salts thereof.

6. 1 - Methyl - 2 - guanidinylidene - imidazolidine and physiologically acceptable acid addition salts thereof.

7. 1 - Ethyl - 2 - (3 - butyl - guanidinylidene) - imidazolidine and physiologically acceptable acid addition salts thereof.

8. 1 - Butyl - 2 - (3 - butyl - guanidinylidene) - imidazolidine and physiologically acceptable acid addition salts thereof.

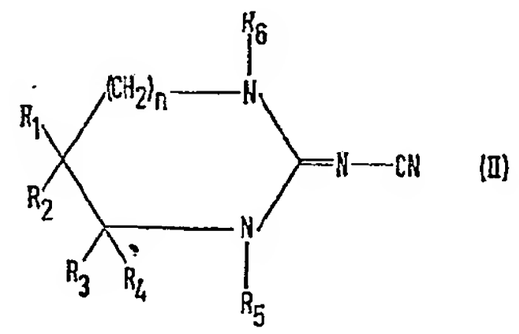
9. 1 - (3,4 - Dichlorobenzyl) - 2 - (3 - adamantyl - guanidinylidene) - imidazolidine and physiologically acceptable acid addition salts thereof.

10. 1 - Butyl - 2 - (3 - butyl - guanidinylidene) - hexahydropyrimidine and physiologically acceptable acid addition salts thereof.

11. Compounds as claimed in claim 1 wherein R_1 to R_6 are as defined in claim 1 and the groups R_7 and R_8 together with the nitrogen atom to which they are attached represent a pyrrolidine, piperidine, morpholine, thiomorpholine, piperazine or hexamethyleneimine ring.

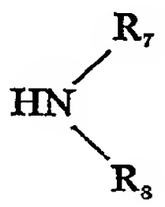
12. Compounds as claimed in claim 1 as herein specifically disclosed with the exception of those as claimed in any of claims 2 to 10.

13. A process for the preparation of compounds as claimed in claim 1 which comprises reacting a cyanimino compound of formula



(II)

wherein the groups R_1 to R_6 and n are as defined in claim 1, with an amine of formula



III

(wherein the groups R_7 and R_8 are as defined in claim 1) or an acid addition salt thereof.

14. A process as claimed in claim 13 wherein an acid addition salt of the amine of formula III is used.

15. A process as claimed in claim 14 wherein the hydrochloride of the amine of formula III is used.

16. A process as claimed in any of claims 13 to 15 wherein the reaction is effected in a melt.

17. A process as claimed in claim 16 wherein the reaction is effected at temperatures of from 80 to 220°C.

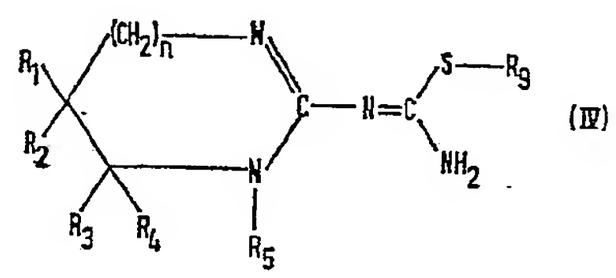
18. A process as claimed in any of claims 13 to 15 wherein the reaction is effected in the presence of a solvent.

19. A process as claimed in claim 18 wherein the solvent comprises water, methyl pyrrolidone, dimethylformamide, quinoline or butanol.

20. A process as claimed in either claim 18 or claim 19 wherein the reaction is effected at temperatures of from 80 to 220°C.

21. A process as claimed in any of claims 13 to 20 for the preparation of the imidazolidine compounds claimed in claim 1 which comprises purifying the said imidazolidine compounds obtained according to any of claims 13 to 20 by converting them into their sparingly soluble crystallisable copper complexes, dissolving these copper complexes in dilute mineral acid and removing the copper present in the solutions by precipitation with hydrogen sulphide.

22. A process for the preparation of compounds of formula I (wherein R_1 to R_5, R_7 and R_8 are as defined in claim 1 and R_6 represents a hydrogen atom) and acid addition salts thereof which comprises reacting an S-alkylthiourea of formula



(IV)

(wherein R_1 to R_5 are as defined in claim 1 and R_9 represents an alkyl group) or an acid addition salt thereof with an amine of formula III as defined in claim 13.

23. A process as claimed in claim 22 wherein a hydrohalic acid addition salt of a compound of formula IV as defined in claim 22 is reacted with an amine of formula III as defined in claim 13.

24. A process as claimed in claim 22 or claim 23 wherein the reaction is effected in the presence of an anhydrous solvent.

25. A process as claimed in claim 24 wherein the anhydrous solvent comprises methanol, ethanol or propanol.

26. A process as claimed in any of claims 22 to 24 wherein the reaction is effected in the presence of an excess of the amine of general formula III as solvent.

27. A process as claimed in any of claims 22 to 26 wherein the reaction is effected at temperatures of from 40 to 150°C.

28. A process as claimed in claim 27 wherein the reaction is effected at temperatures of from 50 to 100°C.

29. A process as claimed in any of claims 13 to 28 wherein an acid addition salt of a compound of formula I (as defined in claim 1) is first obtained and is subsequently converted into a compound of formula I.

30. A process as claimed in any of claims 13 to 28 wherein a compound of formula I (as defined in claim 1) is first obtained and is subsequently converted into a physiologically acceptable acid addition salt thereof.

31. A process as claimed in any of claims 13 to 30 substantially as herein defined.

32. A process for the preparation of compounds as claimed in claim 1 substantially as herein described in any of Examples 1 to 104.

33. Compounds as claimed in claim 1 when prepared by a process as claimed in any of claims 13 to 32.

34. Pharmaceutical compositions comprising as active ingredient at least one compound of general formula I as defined in claim 1 or a physiologically acceptable acid addition salt thereof in association with a pharmaceutical carrier or excipient.

35. Compositions as claimed in claim 34 in a form suitable for topical or oral administration.

36. Compositions as claimed in claim 34 or claim 35 in the form of ointments, tinctures, creams, lotions, tablets or coated dragées.

37. Compositions as claimed in any of claims 34 to 36 in the form of dosage units.

38. Compositions as claimed in claim 37 for oral administration wherein each dosage unit contains from 20 to 100 mg of active ingredient.

39. Compositions as claimed in any of claims 34 to 36 for local administration where-

in the concentration of active ingredient is from 0.5 to 5% by weight.

40. Compositions as claimed in claim 34 substantially as herein disclosed.

41. Pharmaceutical compositions substantially as herein described in any of Examples I to V.

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